REMARKS

Applicant has carefully studied the final Office Action dated August 12, 2010, having a shortened statutory period for response set to expire on November 12, 2010. These explanatory remarks are believed to be fully responsive to the Action. Accordingly, this important patent application is now believed to be in condition for allowance.

Examiner Interview Summary

Applicant thanks Examiner Kim for the interview held with Applicant's representative, Robert Varkonyi, on November 8, 2010. During the interview, the proposed claims revisions were discussed, as they relate to addressing the Office's concern on antecedent basis. Examiner Kim also suggested including information on the non-cultured status of the cells. The new matter rejection was also discussed, in particular the variations of the invention embodied in Examples 1 and 2. Applicant gratefully acknowledges the assistance of Examiner Kim and has amended the claims as suggested.

Statements Regarding DiGiusto, et al. Reference

Applicant has reviewed *DiGiusto, et al.* and respectfully notes that the reference focuses on addressing whether engraftment using umbilical cord blood requires *ex vivo* expansion of cells and whether such expansion is practical.[1] Thawed cells were used as a baseline to compare expanded cells, finding that administering CD34-enriched cells improved hematopoietic reconstitution,[2] specifically for reconstitution of bone marrow.[3] Applicant submits that *DiGiusto, et al.* focused only on proliferation and lineage potential of cells, concluding that "it is reasonable to assume that ex vivo manipulations will be required for most clinical applications."[4]

As noted in the last response, *Pittenger, et al.*,[5] *Edelberg, et al.*,[6] and *Lim, et al.*[7] used cultured cells, and *Pittenger, et al.* specifically provided a detailed disclosure on culturing with

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[1] *DiGiusto, et al.*, Hematopoietic potential of cryopreserved and ex vivo manipulated umbilical cord blood progenitor cells evaluated in vitro and in vivo. Blood. 1996 Feb 15;87(4):1261-71; page 1261, column 1.
[2] *DiGiusto, et al.*, Hematopoietic potential of cryopreserved and ex vivo manipulated umbilical cord blood progenitor cells evaluated in vitro and in vivo. Blood. 1996 Feb 15;87(4):1261-71; page 1266, column 2.
[3] *DiGiusto, et al.*, Hematopoietic potential of cryopreserved and ex vivo manipulated umbilical cord blood progenitor cells evaluated in vitro and in vivo. Blood. 1996 Feb 15;87(4):1261-71; page 1267, columns 1-2.
[4] *DiGiusto, et al.*, Hematopoietic potential of cryopreserved and ex vivo manipulated umbilical cord blood progenitor cells evaluated in vitro and in vivo. Blood. 1996 Feb 15;87(4):1261-71; page 1268, column 1.
[5] Pittenger, et al. (U.S. Pat. No. 6,387,396); column 2, lines 10-14.
[6] Edelberg, et al. (P.G. Pub. 2003/0091547); page 9, paragraphs [0120], [0121]; page 2, paragraph [0018].

fusigens and other cell culturing techniques.[8] The culturing of cells for growth or to artificially differentiate the cells, alters the cell composition from uncultured cells,[9] such as genetic alteration in culture.[10] However, *DiGiusto, et al.* did not analyze the genetic changes in the cells upon *in vitro* growth or *ex vivo* manipulation.

DiGiusto, et al. also stated that "cryopreserved LDMNC samples [were tested] immediately after thawing … only one of 50 grafts injected showed donor reconstitution[.]"[11] This is supported by previous studies by *Nishiyama, et al.*, using cells after immediately thawing cryopreserved UCBCs which failed to transdifferentiate into cardiomyocytes,[12] and *Urbich, et al.*, which noted that freshly isolated bone marrow or blood derived mononuclear cells poorly augmented neovascularization even though the cells efficiently augment vascularization when cultured.[13] In the present invention, Applicant notes that the umbilical cord blood was isolated (using lymphocyte separation medium) and administered to a patient.[14] The administration of cells to infracted mice resulted in a marked improvement of left ventricular fraction shortening over infarct-only mice (20% to 15±3% for infarct versus a low of 26±3% to a high of 34±3% for hUCBC treated infarct), though slightly less than non-infarct controls (44±2%).[15]

Determining the differences between the prior art and the claims, requires an analysis as to whether the claimed invention as a whole would have been obvious, and not just the differences themselves.[16] Applicant submits that the information in *DiGiusto, et al.*, augments the previous statements regarding the use of non-cultured cells.

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[7] Lim, et al. The number of nucleated cells reflects the hematopoietic content of umbilical cord blood for transplantation. Bone Marrow Transplant. 1999 Nov;24(9):965-70; page 966, column 2.
[8] Pittenger, et al. (U.S. Pat. No. 6,387,396); column 3, lines 35-67.
[9] See, Urbich, et al. Endothelial Progenitor Cells: Characterization and Role in Vascular Biology. Circ Res. 2004 Aug 20;95(4):343-53; page 344, column 2 ("[S]pecifc problem arises when cells are ex vivo expanded and cultured because the culture conditions (culture supplements such as FCS and cytokines, plastic) rapidly change the phenotype of the cells.").
[10] See, Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 2 (discussing problems with embryonic stem cells and noting genetic alterations in long-term cultures).
[11] *DiGiusto, et al.*, Hematopoietic potential of cryopreserved and ex vivo manipulated umbilical cord blood progenitor cells evaluated in vitro and in vivo. Blood. 1996 Feb 15;87(4):1261-71; page 1266, column 2.
[12] Nishiyama, et al. The significant cardiomyogenic potential of human umbilical cord blood-derived mesenchymal stem cells in vitro. Stem Cells. 2007 Aug;25(8):2017-24. Epub 2007 May 1; page 2022, column 1.
[13] Urbich, et al. Endothelial Progenitor Cells: Characterization and Role in Vascular Biology. Circ Res. 2004 Aug 20;95(4):343-53; page 345, columns 1-2.
[14] Page 23, paragraph [079]; page 24, paragraph [081] of the Application.
[15] Pages 24-25, paragraph [083] of the Application.
[16] MPEP 2141.02(I) (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 U.S.P.Q. 871 (Fed. Cir. 1983)) (emphasis in original).

Claim Rejections - 35 U.S.C. § 112

Claims 1 and 5-11

Claims 1 and 5-11 stand rejected under 35 USC 112, second paragraph for failing to particularly point out and distinctly claim the subject matter of the invention. The Office found the limitation of "the human umbilical cord blood cell" to lack antecedent basis.[17] Applicant thanks the Office for bringing to Applicant's attention the lack of antecedent basis in claim 1, and has amended the claim to refer to the composition of UCBCs.

Accordingly, Applicant respectfully requests the Office withdraw the 35 USC 112, second paragraph rejection of claims 1 and 5-11.

Claims 1 and 5-11

Claims 1 and 5-12, 14, 16-18 stand rejected under 35 USC 112, first paragraph for failing to comply with the written description requirement. The Office found that the new limitation that the hUCBCs were not cultured prior to administration lacks adequate support in the specification.[18]

Applicant respectfully notes that Example 1 administers the composition to male Sprague-Dawley rats, surgically infarcted.[19] Umbilical cord blood was collected and mononuclear cells isolated.[20] The mononuclear cells were washed, counted, and suspended in fetal bovine serum and DMSO.[21] Further, the Application states that some embodiments of the invention are compositions of hUCBC "in combination with plasma or fetal bovine serum, and DMSO."[22] Moreover,

> [c]ells of the subject invention can be administered in the form of intact umbilical cord blood or a fraction thereof (such term including a mononuclear fraction thereof or a fraction of mononuclear cells[)] … The compositions according to the present invention may be used without treatment with a mobilization agent or differentiation agent ("untreated" *i.e.*, without further treatment in order to

[17] Page 2 of the final Office Action, dated August 12, 2010.
[18] Page 3 of the final Office Action, dated August 12, 2010.
[19] Pages 22-23, paragraph [077] of the Application.
[20] Page 23, paragraphs [078]-[079] of the Application.
[21] Pages 23-24, paragraph [079] of the Application.
[22] Page 13, paragraph [041] of the Application. See also, page 10, paragraph [031] of the Application ("In a further embodiment, the umbilical cord blood composition comprises a mononuclear cell fraction isolated form human umbilical cord blood; plasma or fetal bovine serum, and DMSO.").

> promote differentiation of cells within the umbilical cord blood sample) or after treatment ("treated") with a differentiation agent or other agent[.][23]

In Example 2, the hUCBCs were plated and grown to 60% confluency.[24] However, in Example 1, the specification does not provide that the hUCBCs were plated. In fact, the specification states that the mononuclear fraction was washed and suspended in DMSO and plasma or fetal bovine serum, as noted above. This is further supported by the specification, which provides that in "one embodiment, the umbilical cord blood composition is prepared by the steps comprising: (a) obtaining whole cord blood from a neonatal umbilical cord; (b) enriching the cord blood for mononuclear cells; and (c) resuspending the cord blood enriched for mononuclear cells with plasma or fetal bovine serum, and DMSO."[25] As noted, Example 1 and the cited passage do not provide for plating the cells, whereas Example 2 does provide for plating. Moreover, Example 1 provides for washing hUCBCs and resuspending the cells in DMSO and plasma or fetal bovine serum, which is the composition provided for other sections of the specification[26] and claims,[27] i.e. a composition of hUCBC and DMSO and plasma or fetal bovine serum. Therefore, Example 1 provides for administering a composition which contains uncultured hUCBCs.

Conclusion

Applicant respectfully requests that a timely Notice of Allowance be issued in this case. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

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[23] Page 16, paragraph [050] of the Application.
[24] Page 25, paragraphs [086] of the Application.
[25] Page 10, paragraph [031]; page 13, paragraph [041] of the Application.
[26] For example, page 8, paragraph [020]; page 10, paragraph [031]; page 13, paragraph [041] of the Application.
[27] For example, claim 25.

Very respectfully,

SMITH & HOPEN

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CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

I HEREBY CERTIFY that this correspondence is being electronically transmitted to the Patent and Trademark Office through EFS Web on November 12, 2010.

/lauren reeves/

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Lauren Reeves

Date: November 12, 2010